CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217110Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 17, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217110
Product Name, Dosage Form, and Strength:	Melphalan Hydrochloride Injection, 90 mg/mL
Applicant/Sponsor Name:	Apotex Inc.
TTT ID #:	2022-2642-4
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on August 7, 2023 for Melphalan Hydrochloride. We reviewed the revised container label for Melphalan Hydrochloride (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous label and labeling review.[a] We note that the Applicant removed the recommended dosage statement and manufactured by information on the container label to accommodate the linear barcode.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Iverson, N. Label and Labeling Review for Melphalan Hydrochloride (NDA 217110). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 AUG 01. TTT ID No.: 2022-2642-3.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 11, 2023

To: Bernetta Lane, DHSc, MBA, RN
Senior Regulatory Health Project Manager
Division of Hematologic Malignancies II (DHM2)

From: Melissa Khashei, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for MELPHALAN injection, for intravenous use

NDA: 217110

Background:
In response to DHM2's consult request dated December 21, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA submission for MELPHALAN injection, for intravenous use.

PI
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 31, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on October 20, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or Melissa.Khashei@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 1, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217110
Product Name, Dosage Form, and Strength:	Melphalan Hydrochloride Injection, 90 mg/mL
Applicant/Sponsor Name:	Apotex Inc.
TTT ID #:	2022-2642-3
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 21, 2023 for Melphalan Hydrochloride. We reviewed the revised container label and carton labeling for Melphalan Hydrochloride (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were communicated by the Division to the Applicant.[a]

2 CONCLUSION

The revised carton labeling is acceptable from a medication error perspective. However, the revised container label is unacceptable from a medication error perspective. The linear barcode is missing on the container label.

3 RECOMMENDATIONS FOR APOTEX INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container label

[a]Lane, B. Information Request for NDA 217110, Melphalan. Silver Spring (MD): FDA, CDER, DHM2 (US); 2023 JUL 11. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806dee14&showAsPdf=true

1. As currently presented, the linear barcode is missing on the container label. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Confirm the location the product's linear barcode on the container label in accordance with 21CFR 201.25(c)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 1, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217110
Product Name, Dosage Form, and Strength:	Melphalan Hydrochloride Injection, 90 mg/mL
Applicant/Sponsor Name:	Apotex Inc.
TTT ID #:	2022-2642-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 15, 2023 for Melphalan Hydrochloride. We reviewed the revised container label and carton labeling for Melphalan Hydrochloride (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The preparation instructions on the carton labeling are inconsistent with the PI. Additionally, the storage information lacks prominence on the container label.

3 RECOMMENDATIONS FOR APOTEX INC.

We recommend the following be implemented prior to approval of this NDA:

A. General comment (Container label and Carton labeling)

[a] Iverson, N. Label and Labeling Review for Melphalan Hydrochloride (NDA 217110). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 APR 03. TTT ID No.: 2022-2642.

1. The strength statement continues to lack prominence. We acknowledge that you have increased the font size of the strength statement on the container label and carton labeling; however the strength statement competes in prominence with the proprietary name. Since this product has a different strength (90 mg/mL) and dosage form (Injection) from other Melphalan Hydrochloride products, lack of prominence of the strength statement may contribute to product selection medication errors. We recommend using boxing to ensure prominence of the strength statement and adequate differentiation between the strengths of other Melphalan Hydrochloride products.

B. Carton labeling

1. As currently presented, the side panel of the carton labeling recommends to, "See enclosed Prescribing Information for additional (b) (4) and administration instructions". However, this product is supplied as an injection and does not require (b) (4) To ensure consistency with the Prescribing Information, we recommend revising the statement, "See enclosed Prescribing Information for additional (b) (4) and administration instructions". to read, "See enclosed Prescribing Information for additional dilution and administration instructions"

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 3, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 217110
Product Name, Dosage Form, and Strength:	Melphalan Hydrochloride Injection, 90 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Apotex Inc.
FDA Received Date:	October 20, 2022
TTT ID #:	2022-2642
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Melphalan Hydrochloride Injection, we reviewed the proposed Melphalan Hydrochloride Prescribing Information, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Apotex Inc., submitted Melphalan Hydrochloride (NDA 217110) on October 20, 2022, a 505(b)(2) application which relies upon the listed drug, Alkeran (Melphalan Hydrochloride) Injection under NDA 020207. The LD Alkeran (Melphalan Hydrochloride) by Apotex Inc., (NDA 020207) has been discontinued in 2021. However, according to Federal Register Alkeran was not discontinued or withdrawn for safety or efficacy reasons. Multiple Melphalan ANDAs are marketed as 50 mg/vial.

The proposed product is being developed as a ready to dilute sterile liquid formulation with a strength of 90 mg/mL.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Apotex Inc. submitted a 505(b)(2) NDA to obtain marketing approval for Melphalan Hydrochloride Injection. As noted above the Listed Drug (LD) for this product, Alkeran

(Melphalan Hydrochloride) Injection NDA 020207 is discontinued. We note the proposed Melphalan Hydrochloride Injection is intended for the same indications and has the same active ingredient, diluted final concentration (0.45 mg/mL), dose (16 mg/m^2) , dosing regimen (2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals), and route of administration (intravenous infusion) as the listed drug LD, Alkeran. However, there are differences in the proposed presentation as Melphalan Hydrochloride will be available in different strengths (90 mg/mL vs. 50 mg/vial) and dosage form (injection vs. For injection). Additionally, both products will be indicated for treatment of malignant diseases; however the Melphalan Hydrochloride also proposes dose reductions of up to 50% in patients with renal insufficiency (BUN ≥30 mg/dL). See Appendix A for product characteristics comparison of the LD Alkeran (NDA 020207) and the proposed Melphalan Hydrochloride Injection product (NDA 020207).

We performed a risk assessment of the proposed container label, carton labeling, and PI to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note areas of the proposed labels and labeling, that could be revised to improve clarity and readability of important information. For the Division, we note the PI lacks clarity in the dosage forms and strengths, preparation, administration, and storage information. We also note abbreviations for the route of administration, the use of error prone symbols, and terminology inconsistent with current labeling practices. For the Applicant, we note prominence of the Rx only statement, terminology inconsistent with the PI, and lack of prominence of the strength statement and storage information. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container label, carton labeling, and PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Apotex Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information and Full Prescribing Information

1. The route of administration is abbreviated as “IV”. Presenting the route of administration as an abbreviation may lead to misinterpretation of the correct

route of administration. We recommend revising the route of administration from "IV" to "Intravenous".

B. Highlights of Prescribing Information

1. We recommend removing the (b) (4) from the dosage and administration section and revising the sentence for clarity and readability. Revise to "Recommended dosage is 16 mg/m^2 intravenously over 15 to 20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals. (2.2)".

2. The preparation instructions are different from other melphalan products; therefore we recommend including the statement, "See Full Prescribing Information for preparation and administration instructions. (2.3)".

C. Full Prescribing Information

1. Dosage and Administration Section

a. Section 2.1 Recommended Dosage (b) (4)

i. We recommend removing the (b) (4) from the dosage and administration section and revising the sentence for clarity and readability. Revise to "The recommended dosage is 16 mg/m^2 intravenously over 15 to 20 minutes at 2-week intervals for 4 doses, then, (b) (4) 4-week intervals.".

b. Section 2.2 Dose Modifications for Renal Impairment

i. We recommend removing the administration precautions, (b) (4)

(b) (4)

[redacted] as this information is redundant with the statement regarding hazardous products in the Section 2.3 Preparation and Administration.

c. Section 2.3 Preparation and Administration

i. The preparation instructions lack clarity, which may lead to product preparation errors. Therefore, we recommend the following revisions:

Reconstitution

a. We recommend revising all instances of the term, [redacted] to "hazardous" to be consistent with current labeling terminology.

b. We recommend relocating the statement, "Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, do not use this product." as the second bullet in the preparation instructions.

c. We recommend revising the third bullet as, "Melphalan [redacted] Injection is light sensitive [redacted] After first use, [redacted] the partially used vial in the original carton to [redacted] store refrigerated at 2ºC to 8ºC [36ºF to 46ºF] for use within 28 days [redacted] Retain vial in original carton until contents are used.

2. Dosage Forms and Strengths

a. We recommend revising the statement, "[redacted] to "Injection: 90 mg/mL melphalan as a clear colorless to yellow solution in multiple-dose vial for dilution." as the salt equivalency statement is not needed in this section.

3. Warning and Precautions and Overdosage

a. Section 5.2 Gastrointestinal Toxicity and 10 Overdosage

i. As currently presented, the dose of Melphalan contains the symbol ">". Error prone symbols may lead to misinterpretation and medication error. We recommend replacing the symbol ">" with the intended meaning.

4. How Supplied/Storage and Handling Section
    a. Melphalan Hydrochloride Injection is a clear colorless to yellow solution supplied in a carton containing one 90 mg/mL multiple-dose vial for dilution."
    b. We recommend revising all instances of the term, [redacted] (b) (4) to "hazardous" to be consistent with current labeling terminology.
    c. We recommend revising the storage information from, "Store melphalan injection at 2°C to 8°C (36°F to 46°F)." to "Store Melphalan Hydrochloride Injection refrigerated at 2°C to 8°C (36°F to 46°F). We also recommend relocating the statement, "Melphalan Hydrochloride Injection is light sensitive. Retain in original carton until use." To proceed after the storage statement.
    d. We recommend revising and relocating the vial storage information after use to Section 2.3 Preparation and Administration.

4.2 RECOMMENDATIONS FOR APOTEX INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)
    1. We recommend revising the route of administration from "For Intravenous Infusion [redacted] (b) (4) to "For Intravenous Infusion After Dilution" for added clarity. We also recommend removing the statement, [redacted] (b) (4) as this statement is no longer needed.
    2. The Rx Only statement appears prominent on the principal display panel. We recommend decreasing the prominence by debolding the Rx Only statement.
    3. We recommend revising the statement, "[redacted] (b) (4)" to "WARNING: Hazardous Drug" in bold red font on the principal display panel of the container label and carton labeling.
    4. The strength statement lacks prominence. Since this product has a different strength (90 mg/mL) and dosage form (Injection) from other Melphalan Hydrochloride products, lack of prominence of the strength statement may contribute to product selection medication errors. Increase the prominence of

the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., Rx only statement).

B. Container Labels

1. We recommend revising the statement, [redacted] to be consistent with current labeling practices.

C. Carton Labeling

1. The Recommended Dosage statement is missing from carton labeling. Add the recommended dosage statement "Dosage: See Prescribing Information." To the side panel in accordance with 21 CFR 201.55.
2. As currently presented, the side panel of the carton labeling contains the statement "See enclosed [redacted] for additional [redacted] and administration instructions". To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement to read, "See enclosed Prescribing Information for additional [redacted] and administration instructions".
3. Revise and bold the storage statement as follows, "Store refrigerated at 2° to 8°C (36° to 46°F). Retain in the original carton until time of use to protect from light." We recommend this to increase prominence of this important information and minimize the risk of the storage information being overlooked.
4. We recommend revising the statements, "After first use, [redacted] To "After first use, retain the partially used vial in the original carton to protect from light and store refrigerated at 2ºC to 8ºC [36ºF to 46ºF] for use within 28 days [redacted] ". Retain vial in original carton until contents are used.
5. As currently presented, the carton labeling does not provide the net quantity of contents. Include the net quantity of contents on the principal display panel of container label and carton labeling by revising the statement [redacted] Multiple-Dose Vial" to "in accordance with 21 CFR 201.62.

6. As currently presented, there is no space for end-users to write the beyond-use date which is the date the opened product must be discarded. Since the product has a different expiration date after opening, the container label should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors. We recommend including space for end-users to write the beyond-use date on the container label. For example:

   Discard after ___/____/____

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Melphalan Hydrochloride received on October 20, 2022 from Apotex Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Melphalan Hydrochloride and the Listed Drug		
Product Name	Melphalan Hydrochloride	Alkeran[a]
Initial Approval Date	N/A	November 18, 1992
Active Ingredient	Melphalan Hydrochloride	
Indication	For the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.	
Route of Administration	Intravenous infusion	
Dosage Form	*Injection*	*For injection*
Strength	*90 mg/mL*	*50 mg/vial*
Dose and Frequency	The recommended dose is 16 mg/m^2 intravenous infusion over 15 to 20 minutes. Melphalan is administered at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals. *Dose Modification for Renal Impairment: Dosage reduction of up to 50% should be considered in patients with renal insufficiency (BUN ≥30 mg/dL)*	The recommended dose is 16 mg/m^2 intravenous infusion over 15 to 20 minutes. Melphalan is administered at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.
How Supplied	*Melphalan hydrochloride injection is supplied in a single carton containing one (1) vial.*	*ALKERAN for Injection is supplied in a carton containing one single-dose clear glass vial*

[a] Alkeran [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2011 JUN 09. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020207s016lbl.pdf.

	Each vial contains a clear colorless to yellow solution in multiple-dose vial for dilution. Each mL contains 90 mg melphalan free base equivalent to 100.75 mg melphalan hydrochloride. (NDC 60505-6258-1).	*of freeze-dried melphalan hydrochloride equivalent to 50 mg melphalan and one 10-mL clear glass.* *vial of sterile diluent (NDC 52609-3001-0).*
Storage	*Store melphalan hydrochloride injection at 2°C to 8°C (36°F to 46°F).*	*Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.*

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Melphalan Hydrochloride labels and labeling submitted by Apotex Inc..

- Container label received on October 20, 2022
- Carton labeling received on October 20, 2022
- Prescribing Information (Image not shown) received on October 20, 2022, available from \\CDSESUB1\EVSPROD\nda217110\0003\m1\us\114-labeling\draft\labeling\proposed-prescribing-information.pdf

F.2 Label and Labeling Images

Container label

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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